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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,689	03/25/2004	Mark Larche	JKJ-005CNRCE	7876

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,689	LARCHE ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 16-29* is/are pending in the application.

4a) Of the above claim(s) *16-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/22/2004 & 02/20/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 02/20/2009 is acknowledged.

2. Claims 1-5 and 16-29 are pending.

3. Claims and 16-29 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-5 are currently under examination as they read on a method of desensitizing a patient to a polypeptide allergen comprising administering to the patient a peptide wherein restriction to DR4 possessed by the patient can be demonstrated for the peptide and the peptide is able to induce a late phase response in an individual who possesses DR4.

5. Acknowledgment is made of applicant's claim for foreign priority based on an applications filed in the United Kingdom on 01/09/1998 and 09/21/1998 It is noted, however, that applicant has not filed a certified copies of the United Kingdom 9800445.0 and 9820474.6 applications as required by 35 U.S.C. 119(b).

6. In view of the amendment filed on 02/20/2009, only the following rejections are maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants are not enabled for a method of **inhibiting an allergic reaction** to **a polypeptide allergen** in an individual comprising administering to the individual patient **an isolated peptide from the allergen**, wherein (i) **the peptide is able to bind a particular restriction to a MHC Class II molecule possessed by the individual, (ii) the peptide induces a late phase response in the individual, and (iii) the peptide has a length of 5 to 50 amino acids and (iv) the polypeptide allergen is an allergen selected from the group consisting of grass, tree and weed (including ragweed) pollens; fungi and moulds; foods; stinging insects, the chironomidae (non-biting midges); spiders, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle and a mammal other than a cat,**

such as dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil of claim 1; wherein **the peptide** is included in a composition containing **a plurality of peptides** of claim 2; wherein the **plurality of peptides** includes **a peptide which binds to a MHC molecule selected from the group consisting of DR2, DR3, DR4 and DR7** of claim 3; wherein the individual possesses MHC Class II DR molecule selected from the group consisting of DR2, DR3, DR4 and DR7 of claim 4; and wherein the individual possesses the MHC Class II molecule DR4 of claim 5 for the same reasons as set forth in the Office Action mailed on 08/20/2008.

Applicant's arguments and Declaration filed by Mark Larche on 02/20/2009 have been fully considered, but are not found persuasive.

Applicants argue that

> "The Claims, as amended, do not encompass "any and all peptides and peptide variants" as objected to by the Examiner. Instead, they encompass isolated peptides from known allergens having defined functional and structural features. Specifically, claim 1, as amended, is drawn to a method of inhibiting an allergic reaction to a polypeptide allergen in an individual comprising administering to the individual *an isolated peptide* from the allergen, wherein the peptide possesses *particular functional features (i.e.,* the ability to bind a particular MHC Class II molecule possessed by the individual and the ability to induce a late phase response in the individual), and *particular structural features (i.e.,* the peptide includes a T cell epitope of a known protein allergen sequence and is 5 to 50 amino acids in length). Accordingly, the breadth of the claims are limited to a particular, well-characterized condition to be treated (i. e., an allergic response) by using particularly defined peptides.
>
> As described in detail below, one of ordinary skill in the art could have identified the peptides encompassed by the claimed methods having the particularly claimed structural and functional features, without undue experimentation, based on the teachings in the specification and knowledge available in the art.
>
> At the time the present application was filed, it was well within the skill of the art to generate a multitude of peptides from a known protein. For example, Geysen *et al.* (PNAS, 81, 3998-4002 (1984) (enclosed as Appendix B)) describe a method; subsequently referred to as "the pin method" or "the Pepscan method," that allows for the rapid, concurrent synthesis on polyethylene rods of hundreds of peptides of sufficient purity for use in ELISAs. Geysen *et al.* used these peptides to map epitopes of foot-and-mouth disease virus coat protein involved in antibody binding. In a later paper, Geysen *et al.* state that "The current methodology requires only basic skills in organic chemistry, and can be used to synthesize more than 2000 peptides (hexapeptides) per 10 working day." They further state that their group "presently tests

about 4000 peptides each working day." (Geysen *et al.,* J. Immunol. Methods, 259-274 (1987) (enclosed as Appendix C)).

Further, numerous genetic manipulations for producing peptides from a known protein sequence were commonplace in the art at the time the present application was filed. Relevant techniques include, for example, the use of restriction enzymes to generate fragments of a nucleic acid molecule encoding the protein of interest; the use of timed exonuclease III and/or Dnase I digestions of a nucleic acid molecule encoding the protein of interest, and the use of the polymerase chain reaction to generate precise fragments of the open reading frame encoding the protein of interest. All of these techniques were being employed at the time of filing and described in the literature (see, for example, Methods in Molecular Biology, vol. 66, Epitope Mapping Protocols (1996) (enclosed as Appendix D))..

Methods of identifying peptides having the particularly claimed functional features were also known. For example, as taught in the present specification at page 7 (lines 15-28) "binding to the given MHC Class II molecule *[i.e.,* possession of a functional T-cell epitope] may be demonstrated directly using suitable samples from the patient... [and] can readily be determined in vitro using methods well known in the art...including the PCR-based methods..." (see, *e.g.,* Olerup & Zetterquist (1992) Tissue Antigens 29:225-235 (enclosed as Appendix E)). Additional methods for identifying T-cell epitope-containing peptides previously known in the art include, for example, Van der Zee *et al.* (Eur. J. Immunol. 19:43-47 (1989) (enclosed as Appendix F)). Specifically, Van der Zee *et al.* modified the Pepscan method (described above) so that the synthetic peptides could be released from the solid phase support, making them available for T cell stimulation assays. Van der Zee *et al.* used this modified technique to finely map a T-cell epitope in the mycobacterial 65 kDa heat shock protein. Likewise, Maeji *et al.* used the Pepscan methodology to map T cell epitopes of tetanus toxin (Maeji *et al.* J. of Immunol. Methods 134:23-33 (1990) (enclosed as Appendix G)). In addition to the Pepscsan method, Houghten taught a method for synthesizing large numbers ofpeptides on standard, amino acid resin that was sealed in packets (the "teabag" method). (H0ughten, R.A. (1985) PNAS, 82, 5131-5135 (enclosed as Appendix H)). Oftung *et al.* utilized the method of Houghten to map human T cell epitopes on the Mycobacterium tuberculosis 65-kilodalton protein antigen. (Oftung *et al.* (1988) J. Immunol 141 2749-54 (enclosed as Appendix I)).

As further taught in the present specification, "[w]hether or not a particular peptide can give rise to a LPR [late phase response] can be determined used methods well known in the art..." (see, *e.g.,* Cromwell *et al.,* "Provocation tests and measurements of mediators from mast cells and basophils in asthma and allergic rhinitis," In: Handbook of Experimental Immunology (4) Chapter 127, Editor: Weir D M, Blackwell Scientific Publications, 1986 (enclosed as Appendix J)).

Based on at least the foregoing, one of ordinary skill in the art could have identified the peptides encompassed by the claimed methods without undue experimentation. Moreover, one of ordinary skill could have predictably used such peptides to practice the claimed method without undue experimentation based on knowledge available in the art in combination with the teachings in Applicants' specification. For example, Applicants teach art-known techniques for administering the peptides (see page 35, lines 5-9), exemplary dosages (see page 36, line 11 through page 37, line 25), and particular formulations suitable for administration (see page34, line 24 through page 36, line 9). Accordingly, the presently claimed methods are fully enabled by the specification and knowledge available in the art.

Further, with respect to the Examiner's assertion that Francis *et al. (Curr. Opin. Allergy Clin. Immunol.* 2005 Dec;5(6):537-43) and Kinnunen *et al. (J. Allergy Clin. lmmunoL* 2007 Apr; 119(4):965-72), cast doubt on the predictability of the presently claimed methods, Applicants respectfully refer to the enclosed Declaration by Dr. Mark Larche. As described by Dr. Larche in the enclosed Declaration, the unfavorable results of the single vaccine trial described on page 538 of Francis *et al.* could have been due to any number of outside factors and do not negate the numerous successful studies described in Francis *et al.* or the general success of peptide immunotherapy as a whole. Further, as also described in the enclosed Declaration, contrary to the Examiner's assertion, Kinnunen *et al.* do not teach that altered peptides are unsuitable for the general treatment of allergies. Notwithstanding, Applicants respectfully note that the

claims, as amended, do not include "altered peptides", but instead encompass isolated peptides from known allergens having defined functional and structural features (as discussed above)."

The Declaration filed by Mark Larche on 02/20/2009 states:

1. I am a British subject of the Department of Medicine, McMaster University, 1200 Main Street West, Hamilton Ontario. L8N 3Z, Canada. I presently have the positions of Professor (Department of Medicine McMaster University), Canada Research Chair in Allergy& Immune Tolerance, GSK/McMaster University Chair in Lung Immunology, and Honorary Professional Research Fellow Imperial College, London, UK. I have been working in the .field of peptide immunotherapy since 1995. My publications in this field are shown in the attached annex.

2. I am one of the inventors named for US Patent Application 10/809,689. I understand that the US Patent Office Examiner has objected that the desensitisation method described in the claims of this patent application lacks enablement, written description and novelty. I have been asked to comment on the Examiner's objections.

3. The work described in US Patent Application No 10/809,689 concerns, desensitisation of subjects against specific polypeptide allergens by administration of peptides derived from the same allergen. The peptides have the property of inducing restriction to a MHC class II molecule in the patient (i.e. have a functional T-cell epitope). The peptides are also able to induce a late phase response in those individuals, which underlies the ability of the peptides to desensitise against the whole allergen.

4. I believe that the documents cited by the Examiner to assert the unpredictability of peptide immunotherapy in the art do not support a conclusion that the claimed methods would not allow for desensitisation against the allergens listed in claim 1.

I understand that the methods require inhibiting of an allergic reaction, and do not require complete abolishment of allergic responses. I believe that the findings made in the field of peptide immunotherapy support the conclusion that peptides can be used to inhibit allergic response against whole allergen.

In regard to the cited document Francis *el al,* which I co-authored, the discussion of cat peptide vaccine clinical trials at page 538 mentioned by the Examiner does not detract from the generally positive conclusions established in this review of the field of peptide immunotherapy as a whole. The Examiner mentions individual studies e.g. Pene *et al* which gave poor results for cat peptide vaccines. In fact, as described in Francis et at., a statistically significant improvement in bronchial allergen tolerance was detected within certain groups. Poor results in individual studies could be due to any number of factors, including deficiencies in the methodology used in a given trial. Evidence of some negative results needs to be read in the general context of the other more successful studies in the field. For example, as stated m page 538, right column, first paragraph of Francis *et al,* Oldfield *et al* (ref 25) reported a study with successful effects in reducing responses to FeldI using cat peptides. Norman *et al* [ref 22] discussed at page 538, fourth paragraph of Francis *et al* also reports improvement of allergic symptoms following cat peptide immunotherapy. Although l understand that use of Fel dl peptides is not being-claimed

nevertheless the data presented in US Patent Application No. 10/809,689 in relation to these peptides reinforces the conclusion that overall, at the priority date, peptide immunotherapy with Feldl was feasible.

Importantly, as discussed further at page 539 of Francis *et al,* second paragraph, investigations into the use of peptide immunotherapy for tolerisation against another allergen, bee venom also resulted in positive findings. In particular studies by Muller *et al* [ref 33] and Tarzi *el al* [ref 34] both show that peptide immunotherapy is predictable in that positive findings for a cat allergen could be replicated for a bee allergen. The overall conclusions of Francis *et al, as* summarised at page 541: conclusions section, are that as a whole, peptide immunotherapy is a predictable art. I therefore believe that it is credible that the claimed methods could be used to reduce allergic responses to any of the specific allergens named in claim 1.

5. The Examiner also cites Kinnunen et al to argue that altered forms of the native peptide sequence of an allergen do not predictably cause desensitisation. In particular, the Examiner notes a discussion of earlier results obtained in clinical trial using variant peptides derived from an autoimmune antigen MBP for treatment of multiple sclerosis, an autoimmune disease. The results obtained in that study are not directly relevant to the claimed methods which relate to allergen therapy, specifically desensitisation against the specific allergens listed in claim 1. The mechanisms underlying T-cell responses in autoimmune disease and allergy, are distinct. It cannot be extrapolated from a negative result in autoimmune disease that altered peptides, would not be effective agents for treatment of allergy therapy. This caveat is noted by the authors of Kinnunen et al at page 6, left column, third paragraph. They state that there is no particular reason to suspect that altered peptides would be ineffective in desensitising against allergens, and that in fact therapy of allergy with altered peptides is likely to be a predictable art. As such Kinnunen et al does not allow the conclusion that altered peptides are not suitable in general for treatment of allergy. Furthermore, the claims require restriction to an MHC class II molecule by the peptide referred to and induction of a late phase response. Thus, any altered peptides that do not have these functional properties, and thus might not lead to desensitisation are not being claimed. I therefore believe that it is credible that altered peptides could be used in methods of desensitisation against the listed allergens.

6. I understand that the Examiner is also of the opinion that the application does not provide adequate information on which particular peptides can be used to desensitise in the claimed methods. However, abundant sequence information is provided in US patent application 10/809,689. Sequence information is provided for the allergens listed in claim 1. This information would readily allow preparation of synthetic peptides from 5 to 50 amino acids in length as claimed. Furthermore, synthetic peptides could readily be subjected to the routine experimentation of the type described in Example 6 so as to identify, whether they are suitable for desensitisation. Therefore, the disclosure of the application does provide the claimed peptides because it provides sequence information from which the sequences of the peptides could be identified by routine means and using the teaching in Example 6."

It remains the Examiner's position that one of ordinary skill in the art would be required to perform undue experimentation in order to identify any and all peptides that would be MHC Class II restricted as recited with the claimed functional characteristics to practice the claimed

invention. It is not routine experimentation to determine the MHC restriction of every peptide of 5-50 amino acids of any known, unknown or variant allergen from grass, tree and weed pollens, fungi and moulds, foods, stinging insects, the chironomidae (non-biting midges), spiders, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle and a mammal other than a cat, such as dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil. It is also not routine experimentation to use the genus of those peptides to inhibit allergies, contrary to Applicant's assertion for reasons set forth in the Office Action mailed on 08/20/2008.

It is the Examiner's position that the references cited in the Office Action mailed on 08/20/2008 are relied upon to establish that the state of the art is unpredictable. Whether there are "any number of outside factors" why a particular allergy therapy technique didn't work is beside the point. If a group of scientists with ordinary skill in the art perform allergen immunotherapy and find that it does not work, then the reference is sufficient to establish that the art of allergen immunotherapy is unpredictable, contrary to Applicant's assertion. The cited references teach that any peptide from any allergen cannot be used to inhibit allergies, contrary to the teachings in the specification and Applicant's arguments to support the genus of methods encompassed by the instant claims. As argued in the Office Action mailed on 08/20/208, Francis et al. specifically teaches on page 538 that cat peptide vaccines are unpredictable because they can be significantly associated with adverse events, vaccination is not significant in comparison to placebo, and that of the some peptide immunotherapies that did work, they were only evident

at a single time point post therapy. The reference, written by an inventor of the instant application states "In summary, whereas such studies generally reported modest improvements in clinical and surrogate outcome measures, treatment was associated with a high frequency of adverse reactions." In addition, the co-inventor and co-author of this reference actually states in the reference that choosing peptides for immunotherapy is difficult (not routine experimentation) (In particular, 'Further peptide vaccine design' section on page 541). The whole reference teaches through many examples that peptide selection in immunotherapy makes a difference to the outcome. Therefore, the Declaration of Mark Larche and Applicant's argument that the art as a whole teaches the predictability of peptide immunotherapy is unpersuasive as predictability is not associated with adverse reactions and clinical outcome failure. Therefore, the Examiner remains unpersuaded that allergen immunotherapy is routine. The Examiner acknowledges that the state of the art is hopeful for the future and has seen limited success. However, successful allergy inhibition procedures are not the norm.

Applicant's assertion that the claims only encompass "isolated peptides from known allergens having defined functional and structural features" is not accurate. The claims encompass any 5 to 50 amino acid peptide of any allergen of grass, tree and weed pollens, fungi and moulds, foods, stinging insects, the chironomidae (non-biting midges), spiders, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle and a mammal other than a cat, such as dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil. This recitation includes variant allergens from any of those allergen sources. A Bet v1 allergen with a cysteine to alanine substitution at a certain position is still a grass allergen and is still

encompassed by the instant claim recitations. Therefore, the Examiner's argument with respect to alterned peptide ligands is relevant to the instant rejection. Altered peptide ligands are routinely used to stimulate responses to antigens to which the patient has been previously exposed. Altered peptide ligands are used to change the type of response generated from the engagement with TCR. Since altered peptide ligands are still encompassed by the instant claim recitations after the amendment filed on 02/20/2009 and may also be presented by MHC II molecules in the patient, it stands to reason that responses generated therefrom are unpredictable to inhibit an allergic reaction. The state of the art shows that the nature of the cell signals induced by APLs is unpredictable. Since the claims encompass peptides of allergen variants, peptides that bear little to no sequence similarity to peptides from native allergens are encompassed. Using such peptides to inhibit allergic reactions to a particular allergen would be upredictable at best.

It remains the Examiner's position that the disclosure in the specification cannot provide enablement for the scope of the instant claims. Therefore, the rejection stands.

9. Claims 1-5 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the same reasons as set forth in the Office action mailed on 03/28/2007.

Applicant is in possession of: the peptides of SEQ ID NO: 1, SEQ ID NO:2 and SEQ ID NO:3 for stimulating T cells in vitro.

Applicant is not in possession of: a method of **inhibiting an allergic reaction** to **a polypeptide allergen** in an individual comprising administering to the individual patient **an isolated peptide from the allergen**, wherein (i) **the peptide is able to bind a particular restriction to a MHC Class II molecule possessed by the individual, (ii) the peptide induces a late phase response in the individual, and (iii) the peptide has a length of 5 to 50 amino acids and (iv) the polypeptide allergen is an allergen selected from the group consisting of grass, tree and weed (including ragweed) pollens; fungi and moulds; foods; stinging insects, the chironomidae (non-biting midges); spiders, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle and a mammal other than a cat, such as dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil** of claim 1; wherein **the peptide** is included in a composition containing **a plurality of peptides** of claim 2; wherein the **plurality of peptides** includes **a peptide which binds to a MHC molecule selected from the group consisting of DR2, DR3, DR4 and DR7** of claim 3; wherein the individual possesses MHC Class II DR molecule selected from the group consisting of DR2, DR3, DR4 and DR7 of claim 4; and wherein the individual possesses the MHC Class II molecule DR4 of claim 5 for the same reasons as set forth in the Office Action mailed on 08/20/2008.

Applicant's arguments filed on 02/20/2009 have been fully considered, but are not found persuasive.

Applicants argue that

"As discussed above, the peptides encompassed by the claimed methods possesses *particular functional features (i.e.,* ability to bind a particular MHC Class II molecule possessed by the individual and induces a late phase response in the individual), and *particular structural features (i.e.,* the peptide includes 5 to 50 amino acids of a known protein allergen sequence).

It is firmly established that a patent specification need not describe information that was well known in the art to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Indeed, the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. In *Capon v. Eshhar,* 418 F.3d 1349, 1357 (Fed. Cir. 2005) (hereinafter *"Capon"),* the Federal Circuit explained that "[p]recedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a *variety offactors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.* Id. at 1359 (emphasis added)." Accordingly, if the art is mature, less written description is required.

Specifically, in *Capon,* the claims at issue were drawn to DNA molecules encoding chimeric cell-surface receptor proteins made up of two portions having art-recognized (known) amino acid and nucleotide sequences. The Federal Circuit vacated the Board of Patent Appeals and Interference's decision invalidating these claims for lack of written description on the grounds that the sequences of the claimed chimeric DNA molecules were not explicitly disclosed in specification. The Federal Circuit held that the written description requirement did not require recitation of the nucleotide sequence of the claimed DNA in the specification because the sequence was already known in the field.

The facts of *Capon* parallel those of the present application. Similar to *Capon,* Applicants Should not be required to describe each and every peptide encompassed by the claimed methods, since techniques for generating and identifying peptides having the particularly claimed structural and functional features were well known in the art at the time of filing the present application. As discussed in detail above with respect to the enablement requirement, numerous techniques and procedures for generating peptides from a known protein sequence were Commonplace in the art. Moreover, techniques for testing whether a given peptide had the particularly claimed functional features *(i.e.,* ability to bind a particular MHC Class II molecule possessed by the individual and the ability to induce a late phase response in the individual), were also routine in the field of peptide immunotherapy.

Accordingly, in view of the standard articulated in *Capon* that less written description is required in a mature, predictable field (such as peptide immunotherapy), in combination with the numerous teachings in Applicant's specification and knowledge available in the art at the time of filing, the present application provides more than adequate written description for the presently claimed methods."

The Declaration filed by Mark Larche on 02/20/2009 states:

1. I am a British subject of the Department of Medicine, McMaster University, 1200 Main Street West, Hamilton Ontario. L8N 3Z, Canada. I presently have the positions of Professor (Department of Medicine McMaster University), Canada Research Chair in Allergy& Immune Tolerance, GSK/McMaster University Chair in Lung Immunology, and Honorary Professional Research Fellow Imperial College, London, UK. I have been working in the .field of peptide immunotherapy since 1995. My publications in this field are shown in the attached annex.

2. I am one of the inventors named for US Patent Application 10/809,689. I understand that the US Patent Office Examiner has objected that the desensitisation method described in the claims of this patent application lacks enablement, written description and novelty. I have been asked to comment on the Examiner's objections.

3. The work described in US Patent Application No 10/809,689 concerns, desensitisation of subjects against specific polypeptide allergens by administration of peptides derived from the same allergen. The peptides have the property of inducing restriction to a MHC class II molecule in the patient (i.e. have a functional T-cell epitope). The peptides are also able to induce a late phase response in those individuals, which underlies the ability of the peptides to desensitise against the whole allergen.

4. I believe that the documents cited by the Examiner to assert the unpredictability of peptide immunotherapy in the art do not support a conclusion that the claimed methods would not allow for desensitisation against the allergens listed in claim 1.

I understand that the methods require inhibiting of an allergic reaction, and do not require complete abolishment of allergic responses. I believe that the findings made in the field of peptide immunotherapy support the conclusion that peptides can be used to inhibit allergic response against whole allergen.

In regard to the cited document Francis *el al,* which I co-authored, the discussion of cat peptide vaccine clinical trials at page 538 mentioned by the Examiner does not detract from the generally positive conclusions established in this review of the field of peptide immunotherapy as a whole. The Examiner mentions individual studies e.g. Pene *et al* which gave poor results for cat peptide vaccines. In fact, as described in Francis et at., a statistically significant improvement in bronchial allergen tolerance was detected within certain groups. Poor results in individual studies could be due to any number of factors, including deficiencies in the methodology used in a given trial. Evidence of some negative results needs to be read in the general context of the other more successful studies in the field. For example, as stated m page 538, right column, first paragraph of Francis *et al,* Oldfield *et al* (ref 25) reported a study with successful effects in reducing responses to FeldI using cat peptides. Norman *et al* [ref 22] discussed at page 538, fourth paragraph of Francis *et al* also reports improvement of allergic symptoms following cat peptide immunotherapy. Although l understand that use of Fel dl peptides is not being-claimed nevertheless the data presented in US Patent Application No. 10/809,689 in relation to these peptides reinforces the conclusion that overall, at the priority date, peptide immunotherapy with Feldl was feasible.

Importantly, as discussed further at page 539 of Francis *et al,* second paragraph, investigations into the use of peptide immunotherapy for tolerisation against another allergen, bee venom also resulted in positive findings. In particular studies by Muller *et al* [ref 33] and Tarzi *el al* [ref 34] both show that peptide immunotherapy is predictable in that positive findings for a cat allergen could be replicated for a bee allergen. The overall conclusions of Francis *et al, as* summarised at page 541: conclusions section, are that as a whole, peptide immunotherapy is a

predictable art. I therefore believe that it is credible that the claimed methods could be used to reduce allergic responses to any of the specific allergens named in claim 1.

5. The Examiner also cites Kinnunen et al to argue that altered forms of the native peptide sequence of an allergen do not predictably cause desensitisation. In particular, the Examiner notes a discussion of earlier results obtained in clinical trial using variant peptides derived from an autoimmune antigen MBP for treatment of multiple sclerosis, an autoimmune disease. The results obtained in that study are not directly relevant to the claimed methods which relate to allergen therapy, specifically desensitisation against the specific allergens listed in claim 1. The mechanisms underlying T-cell responses in autoimmune disease and allergy, are distinct. It cannot be extrapolated from a negative result in autoimmune disease that altered peptides, would not be effective agents for treatment of allergy therapy. This caveat is noted by the authors of Kinnunen et al at page 6, left column, third paragraph. They state that there is no particular reason to suspect that altered peptides would be ineffective in desensitising against allergens, and that in fact therapy of allergy with altered peptides is likely to be a predictable art. As such Kinnunen et al does not allow the conclusion that altered peptides are not suitable in general for treatment of allergy. Furthermore, the claims require restriction to an MHC class II molecule by the peptide referred to and induction of a late phase response. Thus, any altered peptides that do not have these functional properties, and thus might not lead to desensitisation are not being claimed. I therefore believe that it is credible that altered peptides could be used in methods of desensitisation against the listed allergens.

6. I understand that the Examiner is also of the opinion that the application does not provide adequate information on which particular peptides can be used to desensitise in the claimed methods. However, abundant sequence information is provided in US patent application 10/809,689. Sequence information is provided for the allergens listed in claim 1. This information would readily allow preparation of synthetic peptides from 5 to 50 amino acids in length as claimed. Furthermore, synthetic peptides could readily be subjected to the routine experimentation of the type described in Example 6 so as to identify, whether they are suitable for desensitisation. Therefore, the disclosure of the application does provide the claimed peptides because it provides sequence information from which the sequences of the peptides could be identified by routine means and using the teaching in Example 6."

It remains the Examiner's position that the specification has not adequately described a correlation between function (inhibiting an allergic reaction, binds to a particular MHC Class II molecule, induces late phase response, binds to a MHC Class II DR molecule selected from the group consisting of DR2, DR3, DR4 and DR7) and structure responsible for inhibiting an allergic reaction, binds to a particular MHC Class II molecule, induces late phase response, and binds to a MHC Class II DR molecule selected from the group consisting of DR2, DR3, DR4 and DR7such that one of ordinary skill in the art would have known what peptides encompassed

by claims could be generated to have the disclosed functions. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. "Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." Ex parte Kubin, 83 U.S.P.Q.2d 1410 (BPAI 2007). The specification does not adequately describe the genus of 5 to 50 amino acid peptides for use in the claimed method for inhibiting an allergic reaction and inducing a late phase response which bind to DR2, DR3, DR4 and DR7 MHC Class II molecules.

Contrary to Applicant's assertion, it was not well known in the art which 5 to 50 amino acid long peptides of all allergens of grass, tree and weed (including ragweed) pollens; fungi and moulds; foods; stinging insects, the chironomidae (non-biting midges); spiders, housefly, fruit fly, sheep blow fly, screw worm fly, grain weevil, silkworm, honeybee, non-biting midge larvae, bee moth larvae, mealworm, cockroach, larvae of Tenibriomolitor beetle and a mammal other than a cat, such as dog, horse, cow, pig, sheep, rabbit, rat, guinea pig, mice and gerbil bind DR2, DR3, DR4 and DR7 MHC Class II molecules and induce a late phase response. Therefore, Applicant has not omitted that which is well known in the art. Further, the specification has not adequately described the genus of such peptides for use in the claimed invention. Therefore, the rejection stands.

A screening method is provided in the instant applicant for identification of peptides which bind to a MHC Class II DR molecule and have the ability to induce a late phase responses.

While discoveries may allow the development of screening assays to identify peptides, the test peptide themselves, have not yet been developed. The instant claims are designed to cover the use of the peptides prior to identification of the peptide themselves.

The instant situation is directly analogous to that which was addressed in *Univ. of Rochester V. G.D. Searle & Co., Inc.*, 358F.3d916, 69 USPQ2d 1886 (fed. Cir. 2004), in which the patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). See MPEP 2163.

10. The following new grounds of rejection are necessitated by the amendment filed on 02/29/2009.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Bungy Poor Fard et al. (PTO-892; Reference U).

Bungy Poor Fard et al. teaches method of inhibiting an allergic reaction to rye grass in an individual (Lol p 1 allergic patients) comprising administering to the individual patient a composition comprising an isolated 12 amino acid peptide of Lol p 1 allergen from rye grass (plurality of peptides), wherein the peptide is able to bind a particular restriction to a MHC Class II molecule possessed by the individual (In particular, page 113 'Study of overlapping peptides in vivo' section, Figure 3, whole document).

The Lol p 1 allergic patients were previously exposed to Lol p 1 allergens. Therefore, the generation of a late phase response in the reference patients is inherent.

The limitations of "wherein the plurality of peptides includes a peptide which binds to a MHC molecule selected from the group consisting of DR2, DR3, DR4 and DR7" of claim 3; "wherein the individual possesses MHC Class II DR molecule selected from the group consisting of DR2, DR3, DR4 and DR7" of claim 4; and "wherein the individual possesses the MHC Class II molecule DR4" of claim 5 are inherent as the same peptide is being administered to the same patient population for the same result. Since the office does not have a laboratory to test the reference peptides, it is applicant's burden to show that the reference peptides are not the peptides recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

13. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Bauer et al. (PTO-892; Reference V).

Bauer et al. teaches method of inhibiting an allergic reaction to birch pollen in an individual (mice) comprising administering to the individual patient (mice) a composition comprising an isolated 14 amino acid peptide of Bet v 1 allergen from birch pollen (plurality of peptides), wherein the peptide is able to bind a particular restriction to a MHC Class II molecule possessed by the individual (In particular, page 537 'Treatment protocol' section, Figures 2 and 5, whole document).

The Bet v 1 allergic mice were previously exposed to Bet v 1 allergens. Therefore, the generation of a late phase response in the reference patients is inherent.

The limitations of "wherein the plurality of peptides includes a peptide which binds to a MHC molecule selected from the group consisting of DR2, DR3, DR4 and DR7" of claim 3 is inherent. Since the office does not have a laboratory to test the reference peptide, it is applicant's burden to show that the reference peptide is not the peptide recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 5, 2009

Nora M. Rooney

Patent Examiner

Technology Center 1600

/Maher M. Haddad/

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Art Unit 1644